Recent updates on the recommendations for the management of ankylosing spondylitis: what and why?

Research in ankylosing spondylitis is a growing field. The recent publication of Assessment in SpondyloArthritis International Society classification criteria has permitted early diagnosis of axial and peripheral spondyloarthritis, which allows early therapeutic interventions. Ankylosing Spondylitis Disease Activity Score has been probed as a useful tool to measure disease activity. Treatment is based on physical therapy and NSAIDs. In refractory cases, the administration of anti-TNF drugs has set a new milestone, as it was shown to be highly effective in radiographic, as well as in nonradiographic, forms of the disease. New biological treatments are being investigated to add new therapeutic options to the armamentarium of the rheumatologist.

KEYWORDS: ankylosing spondylitis/therapy ■ ASAS ■ biological agents ■ classification criteria ■ MRI ■ physical therapy ■ spondyloarthritis ■ TNF-α inhibitor

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Ankylosing spondylitis (AS) is a chronic, inflammatory rheumatic disease, generally starting at a young age. AS is the prototype of the axial form of the spondyloarthropathies [1]. Inflammation and new bone formation in the sacroiliac joints and the spine is the hallmark of AS. Treatment options for AS have been broadened since the introduction of anti-TNF-α agents as effective treatment in fighting activity of the disease, controlling the symptoms in the spine and sacroiliac joints [2]. Clinicians need to be aware of the benefits and risks of the available treatments, and need to have evidence-based information about the most efficacious strategies in daily life practice. In the past few years, we have witnessed remarkable progress in both the understanding of the natural history and pathophysiology of AS and also in the management of the disease. The latter aspect includes the elaboration by the Assessment of SpondyloArthritis International Society (ASAS) of new classification criteria for axial spondyloarthritis (SpA) [3], which makes early diagnosis possible, detecting nonradiographic SpA forms. Frequently, in the field of rheumatology, the same criteria are used for both classification of the patients and for diagnosis of the disease. In 2004, Rudwaleit *et al.* proposed a diagnostic algorithm for axial SpA based on the calculation of likelihood ratios for the clinical, laboratory and imaging parameters that can be applied for preradiographic and radiographic SpA [4].

Major advances in the management of AS have also been made since the introduction of MRI, which enables the monitoring of the extent of acute and chronic lesions in the spine and sacroiliac joints [5]. Radiographic damage is an important target for therapeutic intervention since it is a major determinant of long-term physical function owing to the ossification process that leads to the formation of syndesmophytes and bony bridges. The preferred method for x-ray scoring of spinal changes in AS patients is the modified Stoke Ankylosing Spondylitis Spine Score, with a range of 0–72 [6]. It has previously been shown that significant x-ray changes of the spine can only be expected after 2 years of disease duration. Radiographic damage, in general, is found to be more severe in men and in patients with hip involvement [7,8].

The development and validation of a new AS Disease Activity Score (ASDAS) deserves special interest. ASDAS was designed by ASAS in analogy with the disease activity score [9], an index used to measure disease activity in rheumatoid arthritis (RA), and is a composite index with continuous measurement properties. The ASDAS formulae combine in a weighted logarithmic manner, three items from the Bath Ankylosing Spondylitis Disease Activity (BASDAI) index (back pain, duration of morning stiffness and peripheral pain/swelling) together with patient global evaluation, all ranging from 0 to 10, and inflammatory parameters (C-reactive protein [CRP] mg/l or erythrocyte sedimentation rate [ESR] mm/h) [10]. The ASAS membership has selected the ASDAS with CRP as the preferred version and with ESR as the alternative version. The four cutoffs for disease activity states were

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selected: <1.3 'inactive disease'; >1.3 and <2.1 'moderate disease activity'; >2.1 and <3.5 'high disease activity'; and >3.5 'very high disease activity' [11].

ASAS has recently published an update of the recommendations for the management of patients with AS [12] based on a literature review with integration of input from patients and a physiotherapist in the project group. As a novelty, these new recommendations introduce four overarching principles (**Box 1**) [12]. The target population was defined as follows: the recommendations apply to all patients fulfilling the modified New York criteria for AS, independent of extra-articular manifestations; patients of all ages, including pediatric patients, were included, and all pharmacologic and nonpharmacologic interventions for AS were taken into account. Although recommendations are directed toward AS patients, the experts agreed that patients with early axial SpA who do not yet fulfill the modified New York criteria for AS are part of the same spectrum of the disease, therefore this recommendation could also be applied to such patients. The axial SpA nomenclature covers patients with chronic back pain who have AS, defined by the presence of definite structural changes on radiographs in the sacroiliac joints, and patients with early or abortive forms of SpA, defined by the presence of sacroiliac inflammation, as detected by MRI, or the presence of HLA-B27, in combination with the presence of other SpA-typical features. The ASAS expert panel discussed several points related to the management of AS, and agreed on defining eleven aspects. The items of the updated recommendations are reviewed below.

General treatment

The treatment should be individualized and the current manifestations of the disease, the general clinical status of the patients, including comorbidities, and psychosocial factors should be taken into account.

Disease monitoring

Given the chronic and progressive nature of AS, there is no doubt of the need to properly evaluate the patient from the first visit, as well as to perform periodic evaluations that allow us to judge and clearly document if the patient improves or worsens with respect to the latest revision. The frequency of evaluation should be individualized. The first evaluation (for diagnosis and monitoring) should include not only a medical history and complete physical examination, but also other types of laboratory tests and spinal x-rays. Radiographic evaluation should not be repeated more frequently than every 2 years, unless the clinical situation of the patient requires so.

Nonpharmacological treatment

Physical therapy

Physiotherapy is the most important nonpharmacological measure in AS management and, for a long time, was the only available treatment [13]. Its main aims are to prevent and/or retard restriction of spinal mobility and the development of disability, and to improve pain and stiffness. Appropriate exercise is crucial in managing AS. The 2010 update in recommendations include education and exercise as part of the global management plan of AS patients. Nonpharmacological treatments may complement drug treatment in order to improve symptoms and function and to prevent deformities. However, evidence of the benefits of education and regular exercise is sparse, and is mainly derived from studies with small sample populations [14]. Therefore, long-term, adequately powered, prospective and randomized studies on the benefits of education and specific physical therapy programs are lacking [15]. Different approaches may be proposed, but it seems that guided and supervised physical therapy is more effective than individual home exercise, leading to improvement in physical function, pain and patient global assessment [14]. Thus, it is recommended that patients with predominant axial disease are managed by a physiotherapist, at least

Box 1. Overarching principles of the management of patients with ankylosing spondylitis.

- AS is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist.
- The primary goal of treating the patient with AS is to maximize long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalisation of function and social participation.
- Treatment of AS should aim at optimal care and must be based on a shared decision between the patient and the rheumatologist.
- The optimal management of patients with AS requires a combination of nonpharmacological and pharmacological treatment modalities.

AS: Ankylosing spondylitis.
Data taken from [12].

in the first years of the disease, in order to learn specific exercises. The rehabilitation program may be efficacious in allowing patients to return to work, which therefore leads to economic advantages. Physiotherapy may be completed with other procedures (balneotherapy or electrotherapy) and can be considered throughout the entire course of the disease. Interventions directed to improve disease-specific patient education, rehabilitation and disease-specific patient associations have been shown to promote self-efficacy, to improve patient's abilities in the management of pain and disability, and to facilitate the adoption of healthy lifestyle behaviors and coping with exercise. Although these beneficial effects have been reported in many rheumatic diseases, there are a few reports of the benefits of education interventions in AS patients.

Management of extra-articular manifestations & comorbidities

Other extrarheumatic manifestations, such as aortic insufficiency, pulmonary fibrosis and renal amyloidosis (which should be called nonconcept-related extrarheumatic manifestations), can occur in a small percentage of AS patients, mostly in longstanding disease, and should be treated similarly to those of other causes. Etanercept had been used as treatment for amyloidotic renal involvement complicating AS, and in uncontrolled case reports it was well tolerated, rapid and highly effective in suppressing proteinuria and stabilizing renal function [16].

Osteoporosis is a frequent manifestation in AS, most probably reflecting both limited mobility of the spine and local and general inflammation. An increased prevalence of axial osteoporosis occurs even in early, mild forms of AS, and the demineralization process continues for many years until advanced stages of the disease [17]. It is important to realize that vertebral fractures in patients with AS are often associated with neurological signs and symptoms [18]. In the past, only conventional therapy, such as bisphophonates, was available in AS patients with osteoporosis.

From a physiopathlogical perspective, the aim to prevent vertebral fractures is not only to prevent bone loss within the vertebrae but also to prevent excessive bone formation around the vertebrae. A pioneering study by Demis *et al.* showed that anti-TNF-α therapies are effective in AS osteoporosis, probably owing to their capacity to inhibit inflammatory response [19]. More recently it was shown that treatment of active AS with TNF blockers induces a rather rapid improvement of bone mineral density after 6 months of treatment with infliximab [20] or etanercept [21] but not with placebo. Currently, there is no existing recommendation on the management of osteopenia and osteoporosis for AS patients as evidence is lacking on these subjects.

In patients with AS and an acute vertebral fracture, a spinal surgeon should be consulted [22]. These are often, but not always, rather acute clinical situations, which may or may not be associated with neurological symptoms.

Pharmacological treatment

NSAIDs

For many years, the only available drugs for treatment of AS were NSAIDs. The efficacy of NSAIDs in AS was well established and improvement of symptoms (such as pain and morning stiffness) within 48 h after NSAID intake or a rapid relapse of pain after discontinuation of the agent is so specific that this has been chosen as an item in the set of classification criteria for SpA by Amor *et al.* in 1990 [23]. NSAIDs have a central role in the treatment of AS, still being considered to be the first-line therapy in patients with axial SpA and established AS due to their high symptomatic activity, since the classical disease-modifying antirheumatic drugs (DMARDs) have either no or a poor effect on the axial involvement [24–26]. In addition, a decrease of CRP level at 12 weeks has been seen in AS patients treated with various NSAIDs [27].

In a large number of studies the efficacy and tolerability of NSAIDs were compared. Most studies showed no significant differences in either efficacy or safety of NSAIDs, although aspirin and salicylates were not very effective. There are also no significant differences in efficacy between short- and long-acting agents or between COX-2 selective and nonselective agents [28,29]; however, only COX-2 are indicated in patients with inflammatory bowel disease (IBD) [30]. Continuous intake of NSAIDs is recommended as it can help patients to perform daily exercises and may prevent flares of disease, but NSAIDs could not control spinal inflammation when assessed with MRI, as shown in one small study [31]. It was also shown that continuous, rather than on-demand, treatment could retard radiographic progression of AS [32]. In a recent analysis by Poddubnyy *et al.*, the authors found a retarded radiographic progression achieved with a high-dose NSAID intake in AS patients, and the effect was most pronounced in patients with both syndesmophytes and elevated CRP levels at baseline [33]. In their analysis, the authors also

used the recently introduced index of NSAID intake [34]. This index accounts for both the dose and duration of NSAID intake, which seemed to be relevant in retardation of radiographic spinal progression since no clear differences in radiographic progression could be found when dose or duration of intake were independently analyzed.

The observed inhibition of new bone formation by NSAIDs can probably be explained by the inhibition of prostaglandins (especially prostaglandin E2) synthesis mediated by COX-2 [35]. Prostaglandin E2 is able to stimulate new bone formation by increasing the replication and differentiation of osteoblasts [36]. Prostaglandins also elevate blood supply to the site of new bone formation by causing vasodilatation and by promoting angiogenesis [37]. Similarly, NSAIDs were able to retard induced ectopic bone formation by bone morphogenetic protein 7 in an experimental mouse model, indicating an important role of COX-2-mediated prostaglandin synthesis in new bone formation [38]. Therefore, continuous intake of high doses of NSAIDs could be preferable, although this may increase the risk of side effects including gastrointestinal, cardiovascular and renal toxicity. An in-depth discussion of these side effects is especially important, since AS is the only chronic rheumatic disease in which continuous treatment with NSAIDs is medically justified, given their high clinical efficacy and given the absence of synthetic DMARD alternatives. The potential cardiovascular, gastrointestinal and other side effects of continuous NSAIDs intake have been investigated in great detail and it was recently suggested that the benefit of such a treatment normally outweighs the risk in AS patients [39]. In a review by Song *et al.*, severe gastrointestinal side effects could be expected in approximately 1–3% of patients per year treated continuously with the classic nonselective NSAIDs, while severe cardiovascular side effects occurred in 1–2% of patients per year whether the nonselective or the COX-2 selective NSAIDs were chosen for treatment [39]. These side effects are dose dependent and are higher in patients with gastrointestinal or cardiovascular risk factors.

The co-occurrence of IBD in patients with AS should be kept in mind when managing AS patients; NSAID therapy can pose a problem in the presence of IBD as the underlying bowel disease can be reactivated [40]. COX-2 inhibitors should also be used with caution in such patients [41].

In patients who maintain disease activity despite treatment with a minimum of two consecutive NSAIDs at a maximum recommended or tolerated anti-inflammatory dose for a minimum of 4 weeks in total, or in those who have a contraindication to such treatment, a TNF-α blocker may be started.

DMARDs & corticosteroids in AS

Conventional DMARDs, which play a dominant role in the treatment of RA, have no proven efficacy for the axial manifestations of AS and only a limited efficacy for the peripheral manifestations [42]. Sulfasalazine is the best investigated DMARD for the treatment of AS. In 2005, a Cochrane review article analyzed 12 randomized controlled trials in which sulfasalazine showed some benefits in reducing peripheral joint symptoms, ESR, and easing morning stiffness, yet no benefit was found in physical function, pain, spinal mobility and disease activity [43]. Results from controlled trials suggested that sulfasalazine can prevent acute uveitis attacks [44], although when compared with etanercept, etanercept was more efficacious [45]. A meta-analysis by the Cochrane database of methotrexate to treat AS concluded that there was no evidence to support its use [46]. Leflunomide was ineffective in a randomized, placebo-controlled trial in patients with AS, showing no difference in the proportion of ASAS20 responders [47]. However, due to economic factors, physicians are forced to use conventional DMARDs in their patients. Although glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered (resistant enthesitis, refractory sacroiliac pain) [48], the use of systemic corticosteroids for axial disease is not indicated.

Therefore, the 2010 updated ASAS/European League Against Rheumatism recommendation in AS patients with symptomatic peripheral arthritis to start TNF blockers is that they should have an insufficient response to at least one local steroid injection, if appropriate, and should normally have had an adequate therapeutic trial of a DMARD, preferably sulfasalazine (**Box 2**).

Anti-TNF-α agents for AS treatment

TNF-α blockers are effective in all the different skeletal AS manifestations, such as spinal and sacroiliac pain, peripheral arthritis, enthesitis and dactylitis. The different TNF-α blockers had similar levels of response in the treatment of AS. Infliximab, etanercept, adalimumab and golimumab reduced AS activity, reflected in a 50% reduction of BASDAI, in up to 50% of the treated patients [49–52].

Since there is no head-to-head trial comparing these drugs, there is no demonstration of the superiority of one agent over another in AS. The retention rate of patients with AS after 1 year of anti-TNF therapy was better than for patients with RA [53]. There is also evidence that the efficacy of anti-TNF therapy lasts for several years [54–56]. The choice of a particular agent should depend on the preference of the patient between subcutaneous injections versus intravenous administration, the risk of tuberculosis reactivation (which is higher with the anti-TNF-α monoclonal antibodies), the presence of specific extra-articular manifestations (e.g., uveitis and IBD) and comorbidities. The evidence of treatment of acute anterior uveitis with TNF blockers is until now limited, and no clear recommendations can be given at present. Recently, data from placebo-controlled trials with TNF blockers to treat AS were analyzed for the incidence of reported flares of anterior uveitis during the treatment. Braun *et al.* showed that anti-TNF therapy (infliximab and etancercept) prevented flares of acute anterior uveitis in patients with severe AS in comparison with placebo-treated patients [57]. Infliximab was more effective than etanercept, although this did not reach statistical significance. A more recent study from France that retrospectively analyzed the frequency of anterior uveitis relapses before and after treatment with any of the three TNF blockers (infliximab, etanercept or adalimumab) in patients with SpA, suggested a difference in the efficacies between soluble TNF receptor and anti-TNF antibody treatments [58]. The study demonstrated that the overall incidence of uveitis flares in SpA patients decreased with anti-TNF treatment with a relative risk of 2.4, but when analyzing each agent it was concluded that soluble TNF receptor treatment did not reduce flares, whereas anti-TNF antibodies greatly reduced flares. The authors also indicated that there were patients who developed uveitis flares during etanercept treatment, and this was not observed during anti-TNF antibody administration.

Infliximab and, more recently, adalimumab were proven effective in IBD [59,60], whereas etanercept treatment failed to provide clinical efficacy [61]. In 2007, Braun *et al.* compiled a survey of all data on flares or new onset of IBD in patients with AS exposed to anti-TNF therapy during different placebo-controlled studies (**Table 1**), and found that flares or new onset of IBD are seldom seen in patients treated with infliximab [62]; however, reactivation, especially of ulcerative colitis, were relatively frequent with etanercept. The presence or absence of psoriasis does not seem to make a difference with regard to TNF-α blockers efficacy on musculoskeletal symptoms [63].

The international ASAS consensus statement for the use of anti-TNF agents in AS patients was updated in 2010 (**Box 2**) [64]. The most important change in the updated recommendation for the use of an anti-TNF agents is that patients who fulfill the ASAS axial SpA criteria can also be treated with anti-TNF agents as this condition is seen as an early stage of the same disease, being defined as nonradiographic SpA [65]. Moreover, it has been shown that patients with axial SpA not fulfilling the modified New York criteria have similar burden of disease than patients fulfilling these criteria. Studies with TNF blockers used in patients with nonradiographic SpA showed similar efficacy compared with those developed in patients fulfilling the modified New York criteria [66]. Moreover, MRI studies showed that these agents may be even more effective in nonradiographic SpA than in those with established disease [67] as anti-TNF agents did not inhibit the radiographic progression (new syndesmophytes formation) in patients with established AS over a 2-year period [68–70]. There are recent studies that found radiographic progression in 21% of patients in the first 2 years, but only in 15% of patients in the following 2 years, among a total of 33 AS patients treated with infliximab over 4 years, indicating that the possible effect of TNF blocker treatment on radiographic progression may be a delayed action in AS [71]. It has become clear in recent years that inflammation and erosive changes of the sacroiliac joint or spine are often present for years before radiographic (chronic) changes develop. MRI has been proven as a powerful tool in recent years for the detection of acute inflammation in the sacroiliac joints and spine, which precedes radiographic changes. The major relevance of MRI in recognition of nonradiographic SpA is reflected by the new axial SpA classification criteria developed by ASAS in which, for the first time, imaging was included as a major criterion

Table 1. Inflammatory bowel disease flares in ankylosing spondylitis patients treated with TNF blockers.

TNF blocker	Patients (n)	Patients/ year (n)	CD flare (n)	CD new (n)	UC flare (n)	UC new (n)
Etanercept	419	619	4	4	5	1
Infliximab	386	618	1	0	0	0
Adalimumab	295	132	1	0	2	0
Placebo	434	150	1	0	1	0

CD: Crohn's disease; UC: Ulcerative colitis.
Data taken from [62].

Box 2. Assessment of SpondyloArthritis International Society 2010 update of recommendations for the use of anti-TNF-α agents in patients with axial spondyloarthritis.

- Diagnosis:
  - Patients fulfilling modified New York criteria for definitive ankylosing spondylitis or the ASAS criteria for axial SpA.
  - Active disease for ≥4 weeks, BASDAI ≥4 (0–10) and positive expert opinion.
- Treatment failure:
  - All patients: should have had adequate therapeutic trial of at least two NSAIDs; defined as at least two NSAIDs over a 4-week period in total at maximum recommended dose, unless contraindicated.
  - Axial disease: no pretreatment with DMARDs required.
  - Peripheral arthritis: one local corticosteroid injection, if appropriate; should normally have had a therapeutic trial of a DMARD, preferably sulfasalazine.
  - Enthesitis: appropriate local treatment.
- Contraindications:
  - Refer to updated consensus statement on biological agents.
- Assessment of disease:
  - ASAS core set for daily practice and BASDAI.
- Assessment of response:
  - 50% improvement in BASDAI or absolute change of 2 units (0–10) and positive expert opinion in favor of continuation.
- Assessment after at least 12 weeks.

ASAS: Assessment of SpondyloArthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DMARD: Disease-modifying antirheumatic drug; SpA: Spondyloarthritis.
Data taken from [64].

that may be either radiographic (as defined by the modified New York criteria) or MRI evidence of sacroiliitis [72], this allows classification of patients with pre- or nonradiographic forms of the disease. MRI has been identified as useful in monitoring the efficacy at treatment response, as it was considered in some studies as an outcome parameter for the assessment of acute inflammatory lesions. Accordingly, MRI scores were developed for the grading of inflammation of both the spine and sacroiliac joints in the assessment of inflammatory activity in AS patients [73,74]. Spinal inflammation, as assessed with MRI, improved substantially after anti-TNF therapy [75]. Recent MRI data indicated that anti-TNF-α cannot completely control inflammatory lesions of the spine in AS patients after continuous treatment with infliximab [76]; however, there was no evidence that syndesmophytes formation was accelerated. Thus, patients with nonradiographic SpA may benefit the most from anti-TNF-α treatment. Long-term evaluation studies will show if early initiation of these drugs will have a positive effect on progression of structural damage.

Response is defined as an improvement of at least 50% or 2 units (on a 0–10 scale) of the BASDAI in addition to an expert opinion that treatment should be continued, not only relying on the patients' subjective symptoms. When a patient fails to achieve clinical response after at least 12 weeks of treatment, discontinuation of anti-TNF-α therapy should be strongly considered. Switching to another TNF-α antagonist in nonresponders has been proven to be effective; among 113 patients with AS receiving anti-TNF-α agents, 13% did not respond and were switched to a second drug. A total of 93% of patients had a significant and sustained response after switching [77]. Antibody formation against the drug could be involved in the phenomenon of loss of response and, therefore, secondary nonresponders may have a greater potential for response to a second TNF blocker than primary nonresponders [78,79]. Predictive clinical and biological factors of response to TNF-α blocking agents have been identified and help clinicians choose an adequate treatment [80]. Factors, such as young age, *HLA-B27* genotype, high CRP level, good functional status and the presence of enthesitis at baseline, predict a good response to anti-TNF-α agents. In addition, widespread inflammation of the spine, as demonstrated by MRI, was identified as a predictor of response to anti-TNF-α treatment [81].

Biological therapies other than anti-TNF-α

There is no current evidence for the efficacy of biological therapies in AS, except for anti-TNF-α drugs. This statement is based on two studies evaluating rituximab and abatacept that did not show convincing response rates in patients who had failed TNF blockers [82,83]. Two clinical trials have evaluated the efficacy of tocilizumab (anti-IL-6 antibody) in the treatment of AS. The first, a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of tocilizumab in patients with AS who have failed treatment with NSAIDs and were naive to TNF

Box 3. Follow-up of ankylosing spondylitis patients.

- General anamnesis and musculoskeletal-relevant (including the spinal morning stiffness) socioeconomic aspects.
- Relevant changes on socioeconomic or labor status.
- Physical examination: general and locomotor system.
- Scales horizontal with numerical descriptors (0–10), alternately VAS (global and night) pain in the last week.
- Scale horizontal with numerical descriptors (0–10), alternately VAS about the assessment of the overall activity of the disease in the last week by the patient.
- Scale horizontal with numerical descriptors (0–10), alternately VAS about the assessment of the overall activity of the disease in the last week by the physician.
- Scales horizontal with numerical descriptors (0–10), alternately VAS on fatigue.
- Joint counts (44 joints).
- BASDAI.
- ASAS.
- BASFI.
- Schober test, finger-to-floor distance, lateral flexion lumbar, thoracic expansion, occiput-to-wall/tragus-to-wall, cervical rotation.
- Validated index of valuation of enthesitis (preferable MASES and Berlin, among others).
- SF-12 or ASQoL.
- Radiology of affected joints every 2 years. More frequently, depending on the activity of the disease or emergence of new symptoms.
- General analysis (hemogram, biochemical and urine), erythrocyte sedimentation rate, C-reactive protein level and others depending on the activity of the disease, appearance of new symptoms and the specific treatment, among others.

ASAS: Assessment of SpondyloArthritis International Society; ASQoL: Ankylosing spondylitis quality of life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; MASES: Maastricht Ankylosing Spondylitis Entheses Score; SF-12: Short Form-12; VAS: Visual analog scale. Data taken from [101].

antagonist therapy, was suspended owing to failure to achieve efficacy. The second, a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of tocilizumab in patients with AS who had an inadequate response to previous TNF antagonist therapy, was also suspended owing to lack of efficacy. Clinical trials using ustekinumab, a monoclonal antibody against IL-12 and -23, secukinumab, an anti-IL-17 antibody and apremilast, an orally available, small molecule drug that specifically inhibits phosphodiesterase 4 (an enzyme that modulates inflammatory cytokines) are being developed.

Surgery

Total hip replacement should be considered, regardless of age, in patients with pain or disability who are not responding to treatment and where there is x-ray evidence of joint damage. Spinal surgery may be of value to correct severe deformity or stabilize the spine.

Follow-up evaluation

During follow-up, on the first visit, a medical history will include (although shorter and directed) physical examination, laboratory analysis (at least: blood count, biochemistry, ESR and CRP) with variable periodicity, radiographic study (with variable periodicity) and an evaluation of the prognosis [101]. If a significant change in the course of the disease occurs, such as acute lumbago, fever or weight loss, causes other than inflammation, such as a spinal fracture or infection, should be excluded.

Box 4. Criteria for active disease.

A diagnosis of active disease is considered if the following requirements are met during a period ≥3–4 months.

- Axial forms:
  - BASDAI ≥4 along with at least one of the following:
  - Patient global assessment ≥4 cm on a 0–10-cm scale.
  - Spinal nocturnal pain ≥4 cm on a 0–10-cm scale.
  - Increase of acute phase reactants (ESR and/or CRP).
- Peripheral forms:
  - Arthritis and/or enthesitis in one or more locations, along with at least one of the following:
  - Patient global assessment ≥4 cm on a 0–10-cm scale.
  - Increase in phase acute reactants levels (ESR and/or CRP).

BASDAI: Bath Ankylosing Spondylitis Disease *Activity Index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate. Data taken from* [101].

Box 3 summarizes the variables to be evaluated during follow-up of patients with AS. The frequency of monitoring should be decided on an individual basis depending on the course of symptoms, severity of disease and treatment.

Evaluation of response to treatment

The treatment of the AS aims to achieve remission of the disease or minimize the inflammatory activity to allow a significant improvement in symptoms and signs of disease, such as joint swelling, pain and stiffness, and to preserve the functional capacity, thus maintaining a good quality of life. Limiting the structural damage would be another desirable objective.

To achieve this and, thus, improve the prognosis of patients, it is essential to make an early diagnosis and start treatment as soon as possible. There are several tools when assessing response to treatment. Remission is defined as the absence of symptoms, signs and any other data indicative of activity of the AS. Box 4 summarizes the definition of active disease.

Conclusion

Substantial progress has been made in SpA management due to the possibility of early diagnosis, novel strategies in measurement of disease activity and new treatments available. New ASAS recommendations on the management of AS regarding biological and nonbiological treatment have been published. As the understanding of the disease continues, new therapeutic interventions are being developed.

Future perspective

Improvement in the early diagnosis of SpA is now possible with the new ASAS classification criteria. Programs aiming to raise SpA awareness among rheumatologists and primary care physicians are still needed. New therapeutic weapons are under investigation that, together with advances in discoveries on the etiopathogenesis of the disease, will shed light in this exciting research field.

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Executive summary

Nonpharmacological treatment

- Physical therapy and daily exercise should be indicated in all patients with ankylosing spondylitis or axial spondyloarthritis.

Management of extra-articular manifestations & comorbidities

- Osteoporosis and other comorbidities should be taken into account when evaluating patients with ankylosing spondylitis or axial spondyloarthritis. Anti-TNF-α treatments showed efficacy in many extra-articular manifestations of the disease.

Pharmacological treatment

- NSAIDs remain to be the gold standard of treatment, and their continuous use could retard radiographic progression in ankylosing spondylitis. No disease-modifying antirheumatic drug therapy showed efficacy in axial forms of the disease. Anti-TNF-α drugs show high efficacy in controlling disease activity and extra-articular manifestations of the disease.

Follow-up & evaluation of response to treatment

- Treatment choice should be made on an individual basis. Tools such as Bath Ankylosing Spondylitis Disease Activity Index, Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Metrology Index and Bath Ankylosing Spondylitis Functional Index could help in optimizing therapeutic strategies.

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▪▪ **The Assessment in SpondyloArthritis international Society (ASAS) provides a comprehensive handbook on the most relevant aspects of the assessments of spondyloarthritis (SpA), covering classification criteria, MRI and x-rays for sacroiliac joints and the spine, a complete set of all measurements relevant for clinical trials and international recommendations for the management of SpA.**

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